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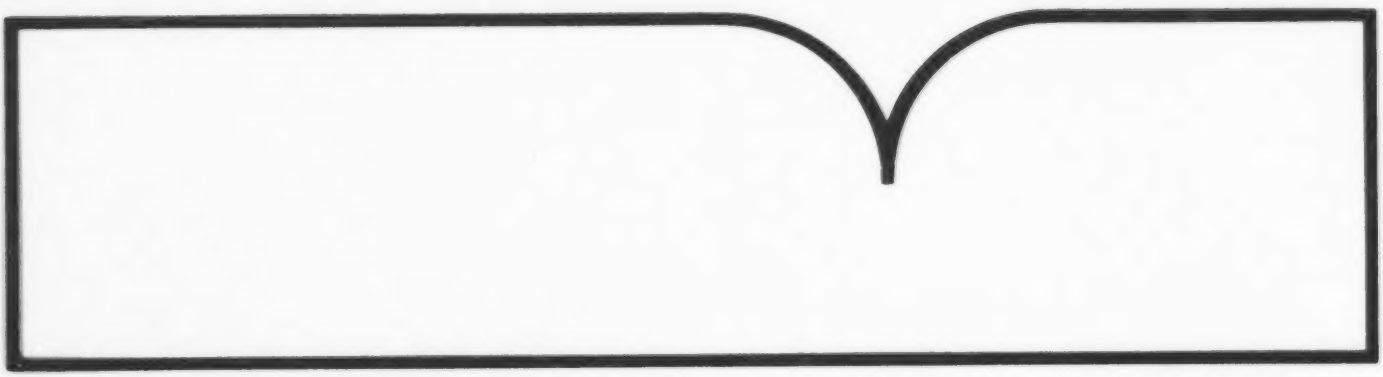

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by

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REGIONAL DEPOSITION OF INHALED MONODISPERSE COARSE AND FINE AEROSOL PARTICLES IN SMALL LABORATORY ANIMALS*

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The regional deposition of inhaled monodisperse insoluble particles of about 1, 3, 5, and 10 μm in activity median aerodynamic diameter was measured in four small rodent species including CF_1 mice, golden Syrian hamsters, Fischer 344 rats and Hartley guinea pigs and in New Zealand rabbits. Near monodisperse aerosols of about 0.05 μm activity median diffusive diameter were also studied. The five species are commonly utilized in inhalation toxicology research. Monodisperse aerosols of fused aluminosilicate particles (2.46 g/cm^3) labeled with radioactive ^{169}Yb were generated utilizing a modified vibrating liquid stream generator, reduced to Boltzmann charge equilibrium with a ^{85}Kr discharge device, concentrated with a centripeter stage, fused in a 1200°C quartz tube furnace, and delivered to a specially designed nose-only exposure system suitable for use with coarse particles as large as 10 μm. Twenty unanaesthetized animals (eight rabbits) were exposed simultaneously for up to 45 minutes to each aerosol particle size. Half were sacrificed immediately after exposure and the remaining half were sacrificed after 20 hours to measure bronchial clearance. Radioassay of selected tissues included the individual lung lobes, trachea, larynx, head airways, and gastrointestinal tract to determine deposition quantities. The results show enhanced nasal-pharyngeal deposition for particles larger than 3 μm in aerodynamic diameter, with over 90 percent nasal-pharyngeal deposition for particles larger than 5 μm. Conversely, pulmonary (alveolar) deposition approaches nil for the larger particles.

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INTRODUCTION

The deposition of inhaled airborne particles in the respiratory airways is a major route of exposure of people to potentially harmful materials in the environment. To evaluate the biological impact of inhaled particles of various types and chemical forms, experiments are usually performed using small laboratory animals, including rabbits and small rodents. Regional deposition data for these laboratory animals are needed to provide the basis of dosimetric interpretation and planning of experiments.

Since the respiratory tracts and breathing of small laboratory animals are different from those of man, the possibility exists that there are also significant differences in the characteristics of deposition of inhaled particles in the laboratory experiments compared to the deposition expected in human populations. This is particularly true for coarse particles larger than 5 μm since such particles may reach the deep lung for people when inhaled orally but are much less likely to reach the pulmonary (alveolar) region when inhaled via the nose. Unlike people, rodents and rabbits are compulsive nose breathing animals, so that their exposure to aerosols is primarily via the nasal route. Hence, such animals may not be desirable inhalation toxicology surrogates for people for coarse particles. Deposition data is available for humans for sizes up to about 15 μm in aerodynamic diameter, but corresponding data have not been available for small laboratory animals.

The deposition of monodisperse aerosol particles in rats and hamsters has been previously studied for aerodynamic diameters up to about 3 μm by RAABE, et al. (1977). This study was undertaken to provide deposition data spanning the same range as reported by RAABE, et al. (1977), but extending as well up to about 10 μm in aerodynamic diameter and also to include mice, guinea pigs, and rabbits.

A new special exposure system was designed, constructed and tested for performing these inhalation studies. Monodisperse aerosols of fused aluminosilicate particles labeled with radioactive ^{169}Yb were used. Deposition was measured in separate lung lobes, tracheobronchial airway and pulmonary (gas exchange) regions of the lung, larynx region, nasal region, and gastrointestinal region. Other organs were also measured to insure the insolubility of the radiolabeled particles.

MATERIALS AND METHODS

Basic Considerations. Monodisperse particles should be nearly identical with respect to shape, composition and size. For the purposes of this study, aerosol radioactivity distributions with respect to aerodynamic resistance diameter, D_{ar}, as described by RAABE (1976) were fit to cascade impactor data utilizing lognormal functions (RAABE, 1978), and were accepted to be sufficiently monodisperse when geometric standard deviations were less than 1.3. For the submicrometer aerosols the activity distributions with respect to diffusive diameters, D_{df}, as described by RAABE (1980) were also measured utilizing a parallel diffusion battery.

Preparation of Aerosols. The monodisperse aerosols used in these studies were prepared using the general methods for generation of fused aluminosilicate particles as described by RAABE et al. (1971). The procedure involved treatment of montmorillonite clay (Osage, Wyoming USA) with peroxide to remove organic components, decanting the finely divided clay suspension, treatment with sodium chloride solution to load the ion exchange sites with sodium cations, dialysis with deionized water to remove excess sodium chloride, and mixing with $^{169}YbCl_3$ with the final clay suspension to allow for ion exchange of the radioactive ^{169}Yb cations into the clay. The resulting suspension was dialyzed and washed with deionized water to remove unexchanged ^{169}Yb.

Monodisperse droplets of about 20 μm were generated with the suspension using an ultrasonic vibrating liquid stream generator based upon the Fulwyler Droplet Generator described by RAABE AND NEWTON (1970). These droplets were dried by heating to about 90°C, passed through a single stage centripeter to concentrate the aerosol and remove excess water and air, and passed through a quartz tube furnace at about 1200°C to collapse the clay lattice (entrapping the ^{169}Yb) and fuse the clay into nearly spherical particles. The resulting aerosol particles (with physical density of 2.46 g/cm^3) were cooled and delivered with diluting air to the animal exposure system. The desired monodisperse sizes were 1, 3, 5, and 10 μm D_{ar}. Representative samples are shown in Figure 1.

In addition to the monodisperse fused aluminosilicate particles, fine submicrometer aerosols were generated from dilute $^{169}YbCl_3$ in water utilizing a Lovelace

nebulizer (RAABE, 1976b). These were nearly monodisperse but had geometric standard deviations exceeding 1.3. Activity median sizes ranged from 0.18 to 0.30 μm D_{ar} and from 0.04 to 0.07 μm D_{df} indicating a physical density about 7 g/cm^3.

Aerosol samples were collected continuously during each exposure in triplicate with filters, in duplicate with cascade impactors, and with a parallel element diffusion battery and assayed using a NaI scintillation auto-gamma counter (Nuclear-Chicago, Inc.) to measure the radioactive ^{169}Yb. Tissue samples were also assayed with the auto-gamma system and with a NaI scintillation crystal connected to a multichannel analyzer. Counter efficiencies were calibrated with respect to sample sizes and the several counters were cross-calibrated.

Exposure Apparatus and Procedures. The first exposures were conducted utilizing the multiport head-only exposure apparatus described by RAABE et al. (1973). However, it was discovered that this apparatus could not be successfully used for particle sizes above 3 μm D_{ar} because of particle losses. A special apparatus that minimized particle losses and facilitated head-only exposures of the animals was designed and built (Figure 2). Animals were separately placed in appropriately sized plastic holders with brass tips through which the nose protrudes into the apparatus during the exposure.

Deposition was studied in five respiratory disease-free animal species (Table 1). Twenty unanaesthetized rodents (eight rabbits) were exposed simultaneously nose-only for up to 45 minutes; half were sacrificed immediately post-exposure and half were sacrificed after 20 hours for determination of pulmonary and bronchial deposition as described by RAABE, et al. (1976). Animals for sacrifice at 20 hours were kept in metabolism cages for collection of excreta. Tissues assayed included blood, larynx, trachea, each right lung lobe, left lung, heart, gastrointestinal tract and contents, liver, kidneys, urinary bladder and contents, headskin, pelt, and carcass. Urine and feces were assayed for the animals sacrificed at 20 hours.

The volumes of air inhaled by each individual resting animal during an exposure was calculated using the Guyton formula (GUYTON, 1947):

$$\text{RESPIRATORY MINUTE VOLUME ml} = 2.1(\text{WEIGHT,g})^{0.75}$$

Typical values are given in Table 2.

RESULTS

A summary of the exposures conducted in this study is given in Table 3. The regional deposition values for the five species are given in Tables 4 through 8, respectively, and shown in Figures 3 through 7. Except for the respiratory tract and GI tract, internal organs were free of ^{169}Yb verifying the inherent insolubility of the aerosol particles and the radiolabel. High total depositions for particle sizes larger than 4.5 μm provided the basis for normalizing to 100% total deposition for these sizes.

DISCUSSION OF RESULTS

The results show an enhanced deposition in the nasal-pharyngeal region for particles larger than 3 μm D_{ar} with corresponding reduction in pulmonary (alveolar) deposition. For sizes approaching 10 μm D_{ar}, pulmonary deposition was effectively nil, while nasal-pharyngeal and laryngeal deposition accounted for essentially all of the inhaled aerosol.

Clearly, the usefulness of these small animal species in toxicological studies where the deep lung and bronchial airways are the principal target is primarily limited to aerosols having particles that are smaller than 3 μm D_{ar}. These species would be useful for sizes larger than 3 μm D_{ar} if the upper airways (especially the nose) were of principal interest.

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TABLE 1. Characteristics of the laboratory animals exposed to monodisperse aerosols in this study.

SPECIES	DESIGNATION	WEIGHT (grams)	AGE (weeks)
CF_1 mouse*	Mus Musculus Crl:CF_1°BR	25 to 35	10 to 15
Golden Syrian hamster*	Mesocricetus auratus Lak:LVG(SYR)	80 to 132	13 to 18
Fischer 344 rat*	Rattus Norvegicus CDF°(F-344)/CrlBR	139 to 271	12 to 21
Hartley Guinea pig*	Cavia porcellus Crl:(HA)BR	293 to 509	5 to 12
New Zealand rabbit**	Oryctolagus cuniculus Hae:(NZW)	2343 to 3475	16 to 32

*The Charles River Breeding Laboratories Inc.,Wilmington, MA 01887 USA

**H.A.R.E. Raabits For Research, Hewitt, NJ 07421 USA

TABLE 2. Typical examples of minute volumes predicted for several mammalian species using the Guyton equation (GUYTON, 1947).

MOUSE	RAT	HAMSTER	GUINEA PIG	RABBIT	DOG	MAN
30 g	250 g	110 g	360 g	2.5 kg	10 kg	70 kg
27 ml	130 ml	70 ml	175 ml	740 ml	2100 ml	9000 ml

TABLE 3. Summary of Inhalation Exposures showing species, exposure date (month/day/year), exposure code number (#), activity median aerodynamic diameter (D_{ar}), geometric standard deviation, (σ_g), aerosol activity concentration (nCi/L) and exposure duration time.

SPECIES	EXPOSURE Date	#	D_{ar} (μm)	σ_g	CONCENTRATION (nCi/L)	TIME (min)
CF_1	12-14-84	44	0.27	1.39	73.3	45
MICE	1-31-85	47	1.09	1.27	136.0	25
	6-28-84	31	3.54	1.22	786.0	10
	2-23-84	19	5.98	1.15	129.1	13
	7-11-84	33	4.49	1.15	111.6	11
	3-08-84	20	9.65	1.16	345.4	20
GOLDEN	12-11-84	42	0.30	1.59	33.3	30
SYRIAN	4-26-83	11	1.00	1.22	152.4	30
HAMSTERS	3-14-83	6	3.11	1.22	22.3	30
	2-02-84	18	5.35	1.18	147.0	15
	5-08-84	26	8.09	1.16	106.4	8.5
FISCHER	12-07-84	41	0.29	1.44	204.4	10
344	4-18-83	10	1.02	1.25	259.7	12
RATS	7-14-83	16	1.03	1.21	39.9	19
	3-10-83	5	3.01	1.16	31.3	30
	3-29-84	22	6.15	1.17	537.1	10
	11-13-84	39	4.26	1.17	154.9	7
	4-03-84	23	10.16	1.12	570.6	8
HARTLEY	12-13-84	43	0.24	1.43	41.9	30
GUINEA	5-04-83	13	0.91	1.20	28.3	24
PIG	7-05-84	32	3.14	1.09	811.8	5
	8-21-84	35	4.06	1.16	1526.3	10
	5-03-84	25	4.95	1.19	443.5	8
	3-15-84	21	8.65	1.15	398.4	9.5
NEW	2-12-85	50	0.18	1.68	29.0	30
ZEALAND	4-14-83	9	1.04	1.27	61.7	23
RABBITS	7-21-83	17	1.09	1.16	218.2	17
	2-05-85	48	0.97	1.28	36.9	15
	2-14-85	51	2.56	1.18	249.1	25
	3-23-83	7	3.22	1.17	7.3	40
	8-02-84	34	2.18	1.14	581.8	5
	9-27-84	36	2.85	1.25	363.5	5
	2-07-85	49	1.94	1.21	119.8	15
	6-13-84	29	4.86	1.09	285.3	10
	6-05-84	28	8.65	1.06	183.9	15

TABLE 4. MEAN DEPOSITION PERCENTAGES AND OBSERVED STANDARD ERRORS OF INHALED MONODISPERSE ^{169}Yb ALUMINOSILICATE AEROSOLS IN CF_1 MICE

Exposure No.	* D_{ar} µm	Lung				Naso-Pharynx		
		Pulmonary	Bronchial	Trachea	Larynx	Skull	G. I.	Total
44	0.27	45.4±4.5	14.0±1.4	0.48±0.08	0.8±0.1	5.4±0.6	4.3±0.6	70.3±7.3
47	1.09	9.7±0.7	5.9±0.4	0.18±0.03	0.8±0.4	4.3±1.1	38.3±5.9	59.2±5.9
31	3.54	0.9±0.2	2.0±0.3	0.7±0.2	2.1±0.7	25.0±8.1	62.8±12.2	93.5±6.5
33	4.49	0.23±0.16	0.89±0.38	0.23±0.08	3.7±2.2	26.9±8.0	68.0±10.0	100
19	5.98	0.4±0.1	0.6±0.3	0.8±0.3	2.3±0.5	59.1±9.5	36.8±9.9	100
20	9.65	0.04±0.01	0.4±0.18	0.26±0.09	3.3±1.0	71.5±9.3	24.5±9.7	100

* Aerodynamic resistance diameter (µm) (Raabe, 1976).

TABLE 5. MEAN DEPOSITION PERCENTAGES AND OBSERVED STANDARD ERRORS OF INHALED MONODISPERSE ^{169}Yb ALUMINOSILICATE AEROSOLS IN GOLDEN SYRIAN HAMSTERS

Exposure No.	* D_{ar} µm	Lung				Naso-Pharynx		
		Pulmonary	Bronchial	Trachea	Larynx	Skull	G. I.	Total
42	0.30	7.5±0.39	12.7±1.4	0.4±0.08	0.3±0.05	1.6±0.2	3.5±0.5	26.1±1.7
11	1.00	9.7±0.4	2.3±0.4	0.06±0.005	0.1±0.03	0.8±0.1	9.8±5.9	22.7±2.1
6	3.11	1.5±0.2	7.1±0.3	1.1±0.3	1.6±0.3	10.9±2.0	64.3±8.2	86.6±7.6
18	5.35	1.7±0.7	3.9±0.01	0.4±0.14	0.26±0.09	4.0±0.8	89.7±3.1	100
26	8.09	0.13±0.03	0.28±0.3	0.60±4.6	1.5±0.7	14.7±5.1	82.7±6.2	100

* Aerodynamic resistance diameter (µm) (Raabe, 1976).

TABLE 6. MEAN DEPOSITION PERCENTAGES AND OBSERVED STANDARD ERRORS OF INHALED MONODISPERSE ^{169}Yb ALUMINOSILICATE AEROSOLS IN FISCHER 344 RATS

Exposure No.	* D_{ar} µm	Lung				Naso-Pharynx		
		Pulmonary	Bronchial	Trachea	Larynx	Skull	G. I.	Total
41	0.29	13.3±0.5	8.1±0.3	0.34±0.03	0.8±0.1	2.7±0.3	1.4±1.0	26.6±0.36
10	1.02	6.5±0.2	4.8±0.2	0.14±0.03	0.5±0.1	2.9±0.4	4.0±0.6	18.9±1.91
16	1.03	11.0±0.3	8.2±0.2	0.14±0.02	1.3±0.3	1.1±0.2	7.6±1.6	29.4±1.9
5	3.11	6.6±0.5	3.9±0.3	0.50±0.08	1.3±0.3	4.0±0.9	82.5±2.3	98.8±0.89
39	4.26	4.8±0.9	11.7±2.2	3.3±2.3	8.9±1.6	31.0±5.4	40.4±7.0	100
22	6.15	1.20±0.11		0.21±0.08	2.4±0.89	25.6±4.7	70.6±5.3	100
23	10.16	0.99±0.43		0.63±0.37	4.3±1.11	83.7±7.7	10.38±8.1	100

* Aerodynamic resistance diameter (µm) (Raabe, 1976).

TABLE 7. MEAN DEPOSITION PERCENTAGES AND OBSERVED STANDARD ERRORS OF INHALED MONODISPERSE ^{169}Yb ALUMINOSILICATE AEROSOLS IN HARTLEY GUINEA PIG

Exposure No.	* D_{ar} µm	Lung				Naso-Pharynx		
		Pulmonary	Bronchial	Trachea	Larynx	Skull	G. I.	Total
43	0.24	26.0±2.6	14.0±4.5	0.25±0.02	0.42±0.05	2.2±0.3	0.73±0.3	43.6±4.5
13	0.91	16.3±0.72	0.64±0.09	0.07±0.02	0.36±0.02	3.0±0.3	2.6±0.7	23.0±1.4
32	3.14	4.7±0.56	0.33±0.76	0.34±0.06	1.1±0.4	18.8±2.6	7.0±1.0	31.9±2.7
35	4.06	2.2±0.65	0.83±0.72	0.08±0.03	0.37±0.11	28.9±5.8	7.1±2.2	38.7±6.5
25	4.95	1.61±0.22		0.53±0.27	0.80±0.25	84.4±3.0	12.7±3.2	100
21	8.65	0.13±0.04	0.22±0.2	2.0±1.2	3.2±1.1	73.4±6.9	21.1±5.8	100

* Aerodynamic resistance diameter (µm) (Raabe, 1976).

TABLE 8. MEAN DEPOSITION PERCENTAGES AND OBSERVED STANDARD ERRORS OF INHALED MONODISPERSE ^{169}Yb ALUMINOSILICATE AEROSOLS IN NEW ZEALAND RABBITS

Exposure No.	* D_{ar} µm	Lung				Naso-Pharynx		
		Pulmonary	Bronchial	Trachea	Larynx	Skull	G. I.	Total
50	0.18	9.3±0.62	9.7±0.64	0.75±0.04	0.80±0.51	3.5±0.9	2.2±0.6	26.1±1.9
48	0.97	4.1±0.59	0.86±0.12	0.13±0.04	0.2±0.09	2.2±0.4	3.4±1.0	10.9±0.87
9	1.04	2.0±0.14	3.1±0.22	0.09±0.05	0.23±0.04	2.7±0.39	4.5±1.4	15.7±1.6
17	1.09	1.9±0.18	1.4±0.14	0.25±0.23	0.11±0.04	1.6±0.42	5.9±1.5	10.9±2.1
49	1.94	0.45±0.01	4.7±0.09	0.20±0.10	1.4±1.2	3.5±0.7	10.5±5.6	20.8±7.1
34	2.18	0.99±0.05	2.4±0.11	0.74±0.21	0.99±0.32	7.2±2.8	7.5±4.82	19.9±7.5
51	2.56	0.22±0.07	3.5±1.0	0.98±0.37	3.42±1.49	7.8±1.0	27.1±10.9	43.0±11.4
36	2.85	0.73±0.15	0.12±0.05	1.92±1.10	0.52±0.16	9.7±3.0	14.3±7.2	28.9±6.3
7	3.22	4.2±0.85	1.7±0.67	0.17±0.08	0.83±0.3	5.0±0.77	27.8±7.8	40.4±8.10
29	4.86	1.1±0.32	8.3±2.3	2.7±1.2	12.8±2.49	22.0±9.6	53.1±10.7	100
28	8.65	0.01±0.0	0.24±0.15	1.4±1.3	1.18±0.23	15.7±2.4	81.5±2.8	100

* Aerodynamic resistance diameter (µm) (Raabe, 1976).

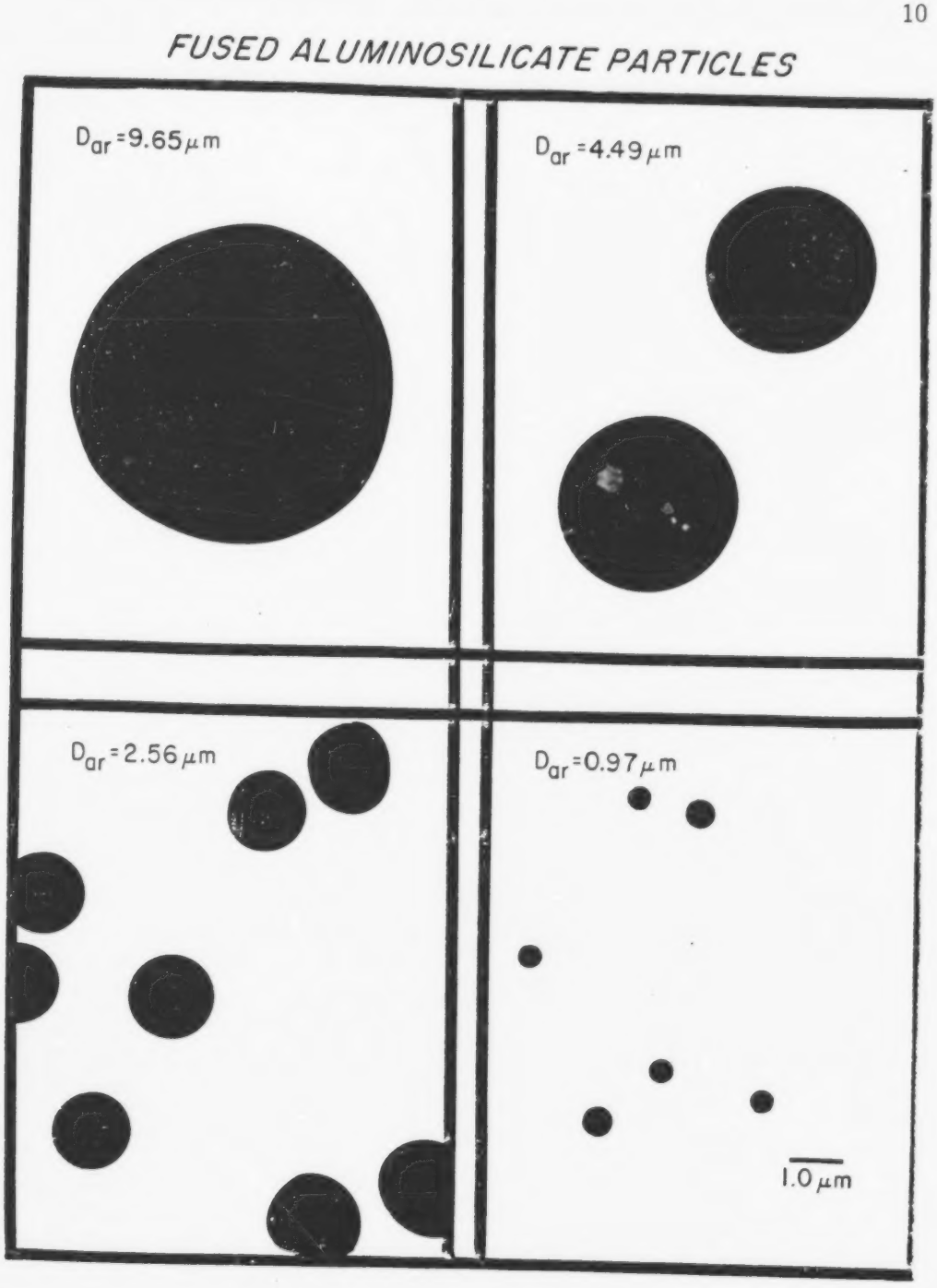

Figure 1. Electron Micrographs of Four Representative Sizes of the Monodisperse ^{169}Yb Labeled Fused Aluminosilicate Aerosol Particles Used in This Study.

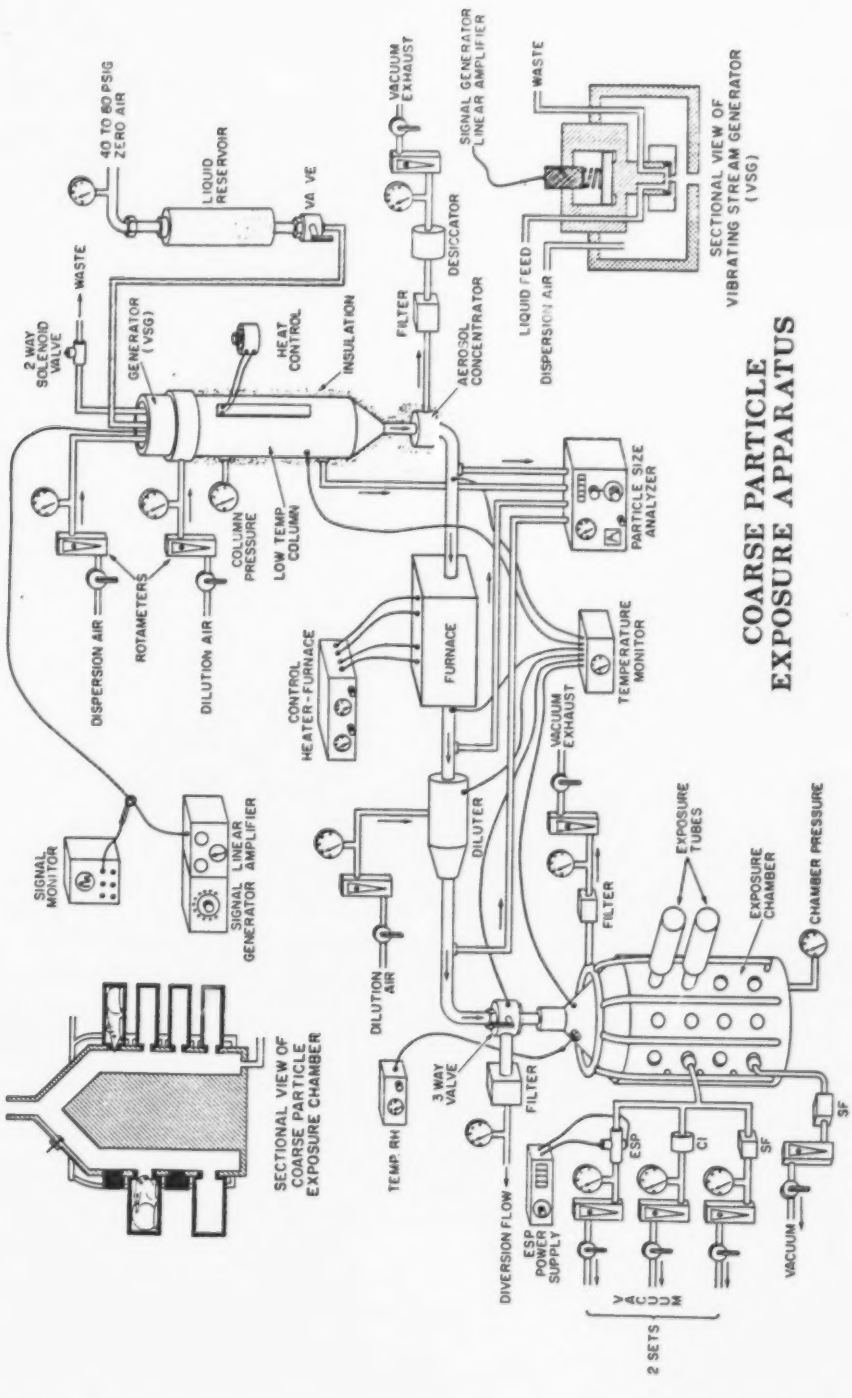

Figure 2. Schematic Illustration of the Special Nose-Only Exposure Apparatus used in the Study to Expose Small Laboratory Animals to Monodisperse Aerosols.

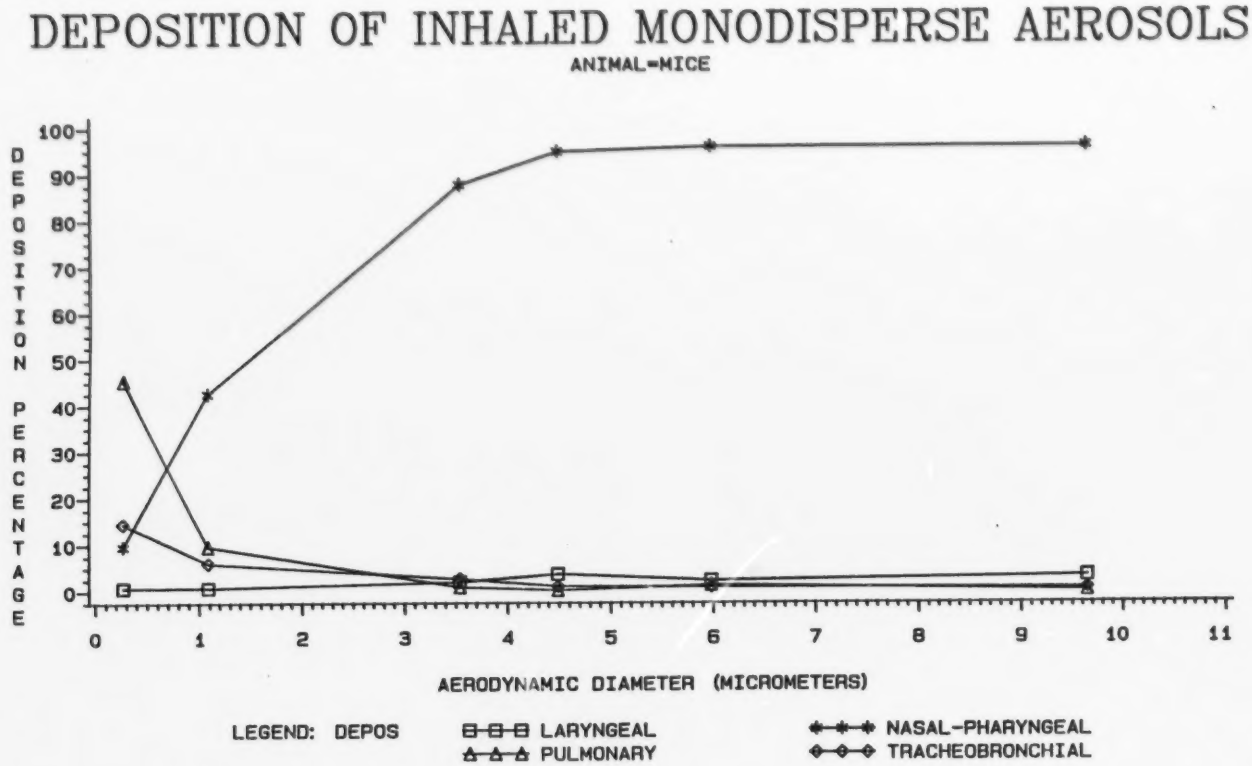

Figure 3. Deposition of Inhaled Monodisperse Aerosols with respect to aerodynamic resistance diameter, D_{ar}, in CF_1 Mice.

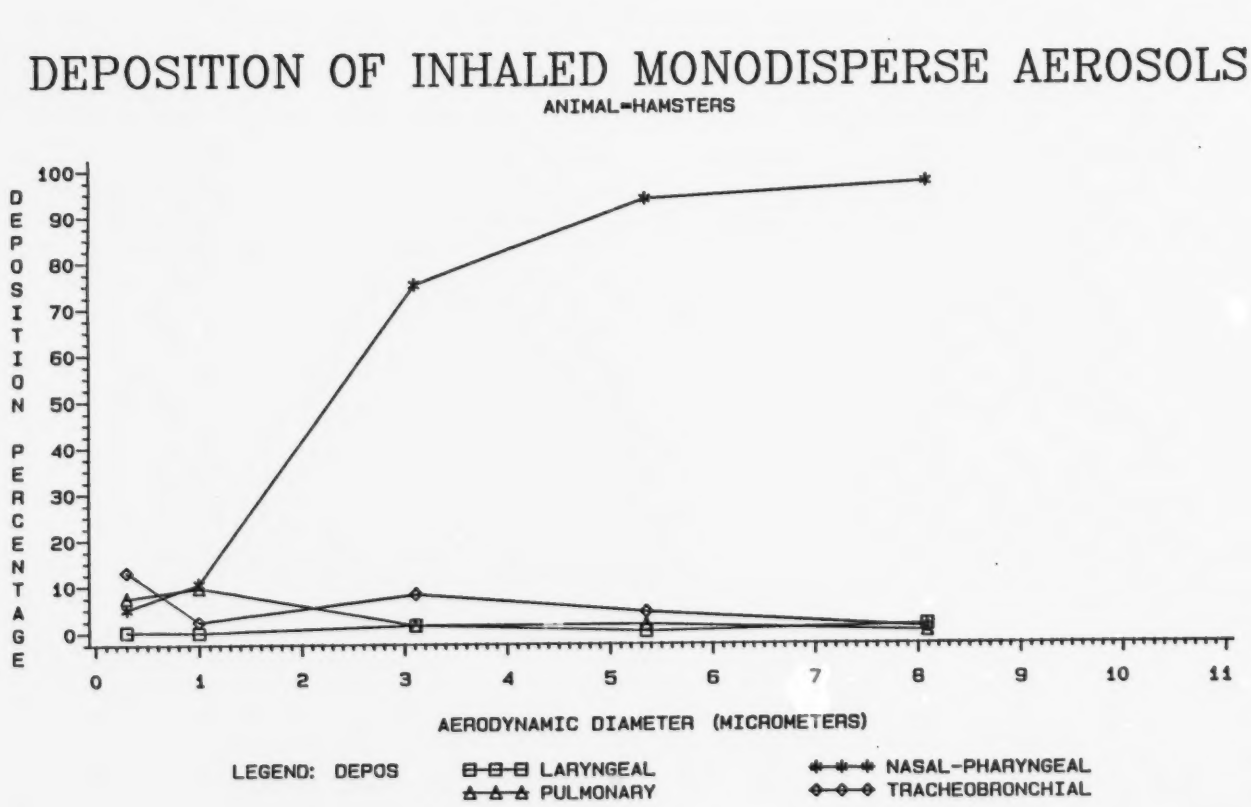

Figure 4. Deposition of Inhaled Monodisperse Aerosols with respect to aerodynamic resistance diameter, D_{ar}, in Golden Syrian Hamsters

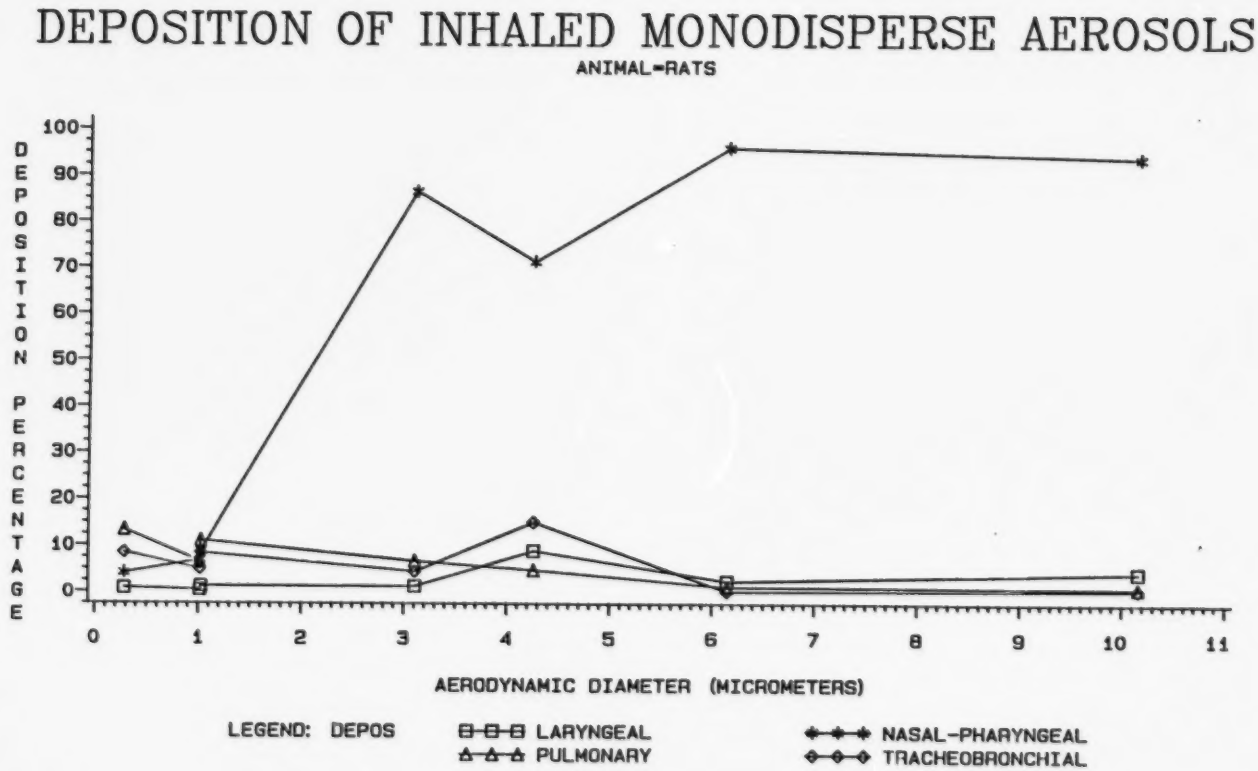

Figure 5. Deposition of Inhaled Monodisperse Aerosols with respect to aerodynamic resistance diameter, D_{ar}, in Fischer 344 Rats.

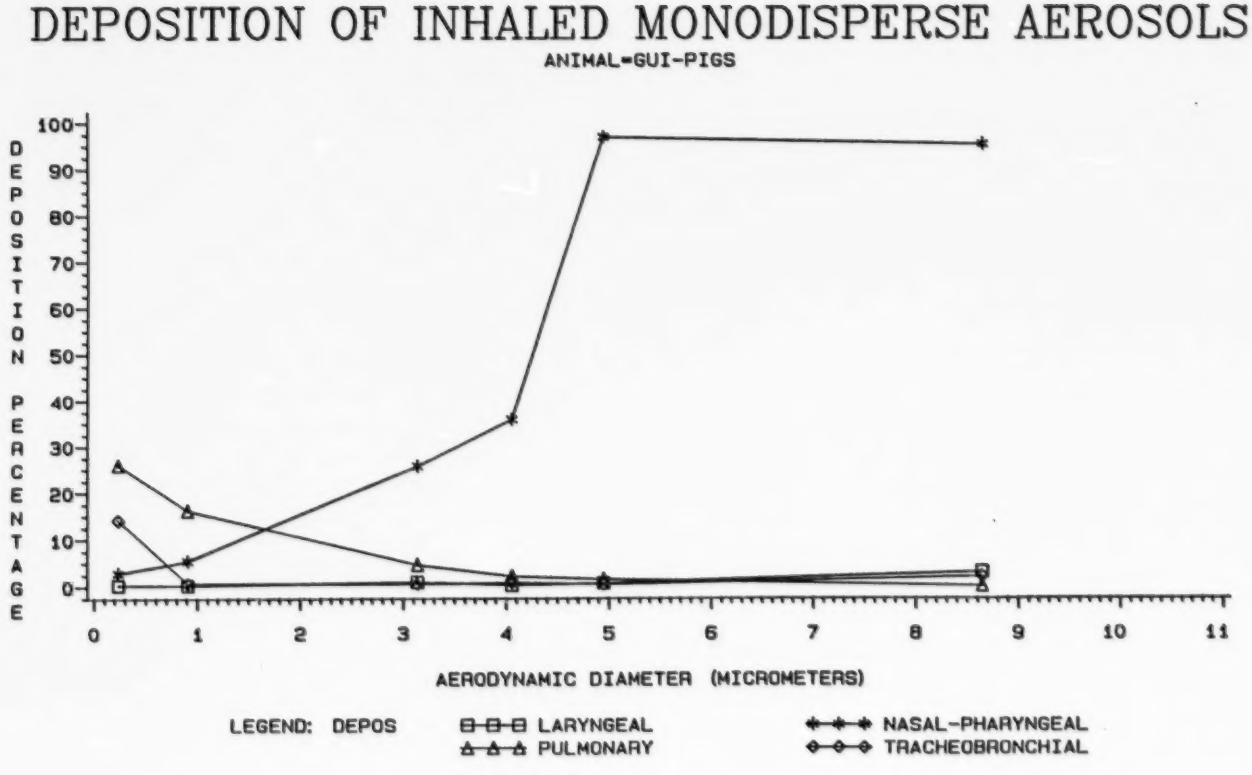

Figure 6. Deposition of Inhaled Monodisperse Aerosols with respect to aerodynamic resistance diameter, D_{ar}, in Hartley Guinea Pigs.

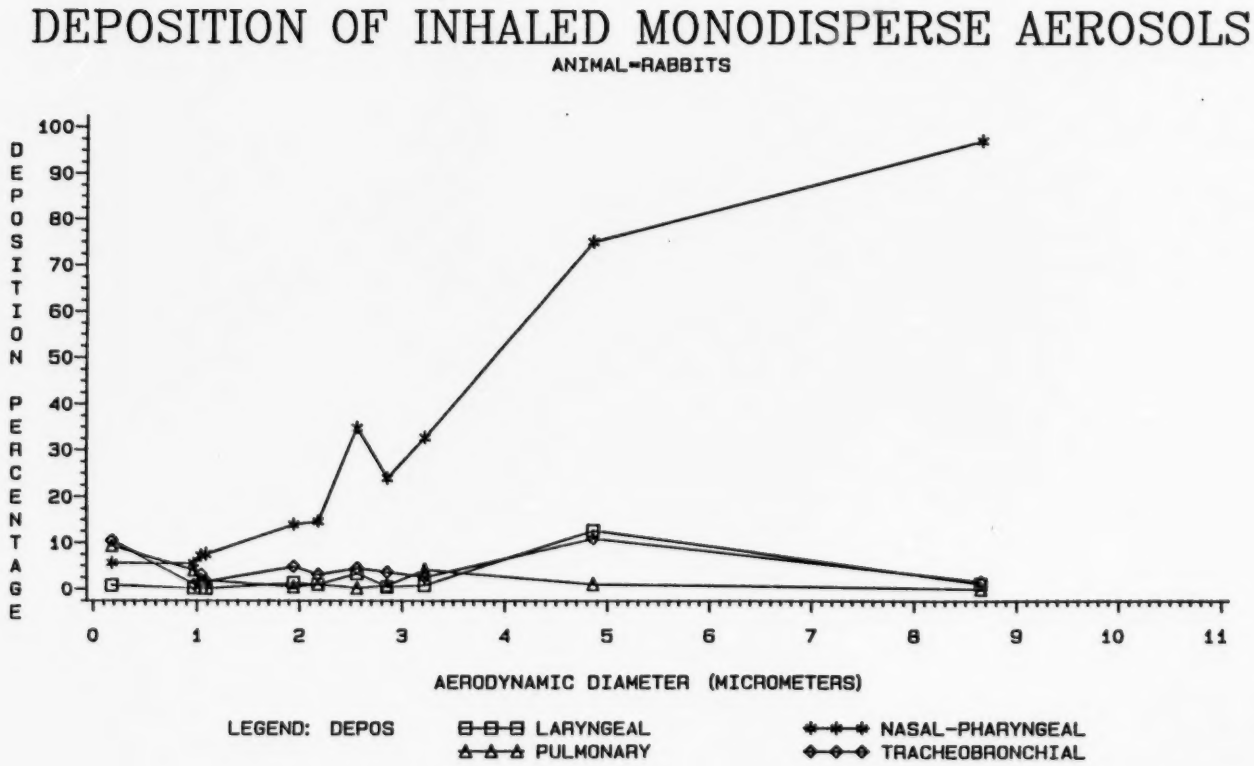

Figure 7. Deposition of Inhaled Monodisperse Aerosols with respect to aerodynamic resistance diameter, D_{ar}, in New Zealand Rabbits.